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Highly chemo- and diastereoselective addition of diethylzinc through intramolecular autoactivation of enantiopure 2-acyl-1-formylferrocene: application to the synthesis of optically pure 1,2-diacylferrocenes

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Abstract

The enantiomerically pure 1,2-diacylferrocenes (+)-(*R*)-**10–12** (ee>99%) were synthesized from (N,N-dimethylaminomethyl)ferrocene via enantiomerically pure 2-acyl-1-formylferrocene (+)-(*R*)-**4–6**. A novel methodology was performed using the chemo- and diastereoselective addition of diethylzinc to the formyl function through an intramolecular autoactivation.

There is still a rapid growth in the search for catalytic asymmetric processes for carbon–carbon bond formation, and a large range of strategies have proved to be successful in providing high levels of enantioselective reactions.[1] In this context, the asymmetric alkylation of aldehydes with organozincs[2] has been one of the most extensively explored reactions and among the catalysts studied, organometallic compounds such as ferrocenyl complexes[3] have shown remarkable results. In some examples, the synthesis of the chiral alcohols has been achieved by autocatalysis[4] or autoinduction[5] in the presence of R_2Zn. Moreover, chemo- and enantioselective alkylation of the formyl group of prochiral keto aldehydes is a versatile method for the synthesis of chiral hydroxy ketones. However, Grignard and alkyllithium reagents, which are widely used carbonyl alkylation agents in organic synthesis, often fail to discriminate effectively between aldehydes and ketones in view of their highly nucleophilic characters, although the chemoselective nonasymmetric alkylation of aldehydes in the presence of ketones has been the subject of considerable attention.[6]

Previously, we have described an intramolecular asymmetric autoactivation in the stereoselective alkylation of 2-(N,N-dimethyaminomethyl)ferrocenylcarboxaldehyde with organometallic reagents[7] and we have developed a novel synthesis of 1,2-diformylferrocene and racemic 2-acyl-1-formylferrocenes from commercially available (N,N-dimethylaminomethyl)ferrocene.[8] Thus, in order to show another

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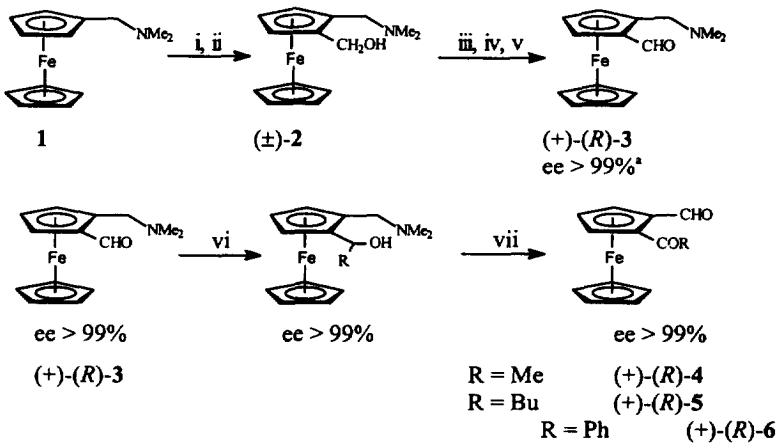
asymmetric self catalyst potential of a substituted ferrocene with planar chirality, we turned our attention to the study of the chemo- and diastereoselective addition of diethylzinc through an intramolecular autoactivation of enantiomerically pure 2-acyl-1-formylferrocene.

In this communication, we describe the synthesis of the enantiomerically pure 2-acyl-1-formylferrocenes (+)-(*R*)-**4–6** and we report the chemo- and diastereoselective addition of the diethylzinc through an intramolecular autoactivation. Finally, we apply this novel methodology to the synthesis of the enantiopure diacylferrocenes (+)-(*R*)-**10–12**. We first carried out the synthesis of the enantiomerically pure compound (+)-(*R*)-**3**[9,10] (ee>99%) from the commercially available (N,N-dimethylaminomethyl)ferrocene **1** via the transesterification of the racemic mixture of (±)-**2** with vinylacetate catalysed by the *Candida rugosa* lipase (CRL) following the literature method[9] (42% isolated yield). The complex (+)-(*R*)-**3** was quantitatively alkylated with various organolithium nucleophiles to give the corresponding aminoalcohols. Finally, oxidation in the presence of MnO_2[8] led to the enantiomerically pure 2-acyl-1-formylferrocenes (+)-(*R*)-**4–6** in 86%, 63%, and 58% yield respectively (ee>99%) (Scheme 1).

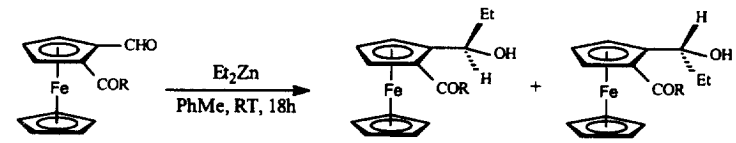


Reagents: i) nBuLi, DMF, 73% yield; ii) $NaBH_4$, 100% yield; iii) CRL (SIGMA, type VII, 835 unit/mg, 1.440 unit/ mg prot.), tBuOMe, vinylacetate, 42% yield; iv) NaOH, 100% yield; v) MnO_2, 100% yield; vi) MeLi or BuLi or PhLi, 100% yield; vii) MnO_2, toluene, reflux for 45 minutes. [a] Determined by ^1H NMR analysis in presence of Pirkle's alcohol.

Scheme 1.

In the presence of Et_2Zn at room temperature,[11] the 2-acetyl-1-formylferrocene (+)-(*R*)-**4** gave a mixture of diastereomers (*R*,1*R*)-**7** and (*R*,1*S*)-**7**[10] in 72% yield (68% de), the 1-formyl-2-(1-oxopentanyl) ferrocene (+)-(*R*)-**5** provided the diastereomers (*R*,1*R*)-**8** and (*R*,1*S*)-**8** in 68% yield (71% de) and the 1-formyl-2-(1-oxobenzyl)ferrocene (+)-(*R*)-**6** gave the diastereomers (*R*,1*R*)-**9** and (*R*,1*S*)-**9** in 38% yield (76% de). This reaction was performed with a high chemoselectivity with regards to the formyl function and with a very good diastereoselectivity (up to 76% de). It is noteworthy that this reaction was carried out in the absence of catalyst. Without any activation Et_2Zn is rather unreactive due to its linear non polar geometry.[2a] Such an activation is realized through a coordinatively unsaturated bent structure. Thus, an activation takes place through participation of the oxygen atoms and is responsible for the selectivities. This is a new example of stereocontrol provided only by the planar chirality. Previously, Soai and coworkers[12] have developed the synthesis of hydroxyketones by chemo- and enantioselective alkylation of achiral ketoaldehydes with dialkylzinc reagent using chiral catalysts. To the best of our

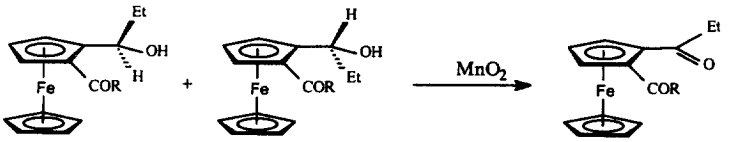
knowledge, this is the first example of a bifunctionnal compound displaying simultaneous diastereo- and chemoselectivities in an autocatalytic reaction (Scheme 2).



R = Me	(+)-(*R*)-**4**	(*R*,1*R*)-**7**	(*R*,1*S*)-**7**
R = Bu	(+)-(*R*)-**5**	(*R*,1*R*)-**8**	(*R*,1*S*)-**8**
R = Ph	(+)-(*R*)-**6**	(*R*,1*R*)-**9**	(*R*,1*S*)-**9**

Scheme 2.

Finally, each mixture of the diastereoisomers **7–9** was oxidized and led to the optically pure 1,2-acylferrocene (+)-(*R*)-**10**,[13] (+)-(*R*)-**11**[14] and (+)-(*R*)-**12**[15] in 82%, 72%, 66% isolated yield respectively (Scheme 3).



R = Me	(*R*,1*R*)-**7**	(*R*,1*S*)-**7**	(+)-(*R*)-**10**
R = Bu	(*R*,1*R*)-**8**	(*R*,1*S*)-**8**	(+)-(*R*)-**11**
R = Ph	(*R*,1*R*)-**9**	(*R*,1*S*)-**9**	(+)-(*R*)-**12**

Scheme 3.

In conclusion, new enantiomerically pure chiral 1,2-acylferrocenes (+)-(*R*)-**10–12** have been prepared. In this synthesis, we have shown and used the chemo- and diastereoselective properties of the 2-acyl-1-formylferrocene through an autocatalytic reaction. Further studies of the separation of the diastereomers **7–9** and their catalytic application in a diethylzinc addition process to benzaldehyde are under development and will be presented in the future.

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10. The nomenclature followed the attribution of the configuration described by previous literature: Schlögl, K. *Topics in Stereochemistry*, **1967**, *1*, 39. The denomination '*S*' or '*R*' refers to the planar chirality and the '1*S*' or '1*R*' one refers to the sp^3 chirality.
11. Typical experimental procedure: 2-Acyl-1-formylferrocene (0.39 mmol) was dissolved in toluene (10 ml) under nitrogen. Diethylzinc (1.6 mmol, 1.1 M in toluene) was added. The mixture was stirred at room temperature for 18 hours. After work-up, the mixture was purified by column chromatography but the diastereomers could not be separated. The ratio was determined by ^{1}H NMR.
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13. (+)-(*R*)-**10**: $[\alpha]_D^{20}$=+757 (c=1.05, $CHCl_3$); dark red oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.2 (s, 1H), 5.0 (s, 1H), 4.8 (s, 1H), 4.3 (s, 5H), 2.9–2.6 (m, 2H), 2.2 (s, 3H), 1.2 (t, J=6.9 Hz, 3H).
14. (+)-(*R*)-**11**: $[\alpha]_D^{20}$=+851 (c=0.55, $CHCl_3$); red oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.2 (s, 1H), 5.0 (s, 1H), 4.9 (s, 1H), 4.3 (s, 5H), 2.9–2.6 (m, 4H), 1.7 (m, 2H), 1.4 (m, 2H), 1.3 (t, J=6.9 Hz, 3H), 1.0 (t, J=7.3 Hz, 3H).
15. (+)-(*R*)-**12**: $[\alpha]_D^{20}$=+1777 (c=0.52, $CHCl_3$); brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0–7.6 (m, 5H), 5.3 (s, 1H), 5.0 (s, 1H), 4.8 (s, 1H), 4.3 (s, 5H), 2.8–2.5 (m, 2H), 1.3 (t, J=7.0 Hz, 3H).